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(54) Title: SUBSTITUTED ALKANOHYDROXAMIC ACIDS AND METHOD OF REDUCING TNF α LEVELS (57) Abstract Imido and amido substituted alkanohydroxamic acids reduce the levels of TNF α and inhibit phosphodiesterase in a mammal. A typical embodiment is 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide.			

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SUBSTITUTED ALKANOHYDROXAMIC ACIDS AND METHOD OF REDUCING TNF α LEVELS

Cross-Reference to Related Application

This application is a continuation-in-part of U.S. patent application Serial No.
5 08/903,975, filed July 31, 1997.

Field of the Invention

The present invention relates to imido and amido substituted
alkanohydroxamic acids, the method of reducing levels of tumor necrosis factor α in
a mammal through the administration thereof, and pharmaceutical compositions of
10 such derivatives.

Background of the Invention

Tumor necrosis factor α , or TNF α , is a cytokine which is released primarily by
mononuclear phagocytes in response to a number immunostimulators. When
administered to animals or humans, it causes inflammation, fever, cardiovascular
15 effects, hemorrhage, coagulation, and acute phase responses similar to those seen
during acute infections and shock states. Excessive or unregulated TNF α production
thus has been implicated in a number of disease conditions. These include
endotoxemia and/or toxic shock syndrome {Tracey *et al.*, *Nature* 330, 662-664 (1987)
and Hinshaw *et al.*, *Circ. Shock* 30, 279-292 (1990)}; cachexia {Dezube *et al.*,
20 *Lancet*, 335 (8690), 662 (1990)} and Adult Respiratory Distress Syndrome where
TNF α concentration in excess of 12,000 pg/mL have been detected in pulmonary
aspirates from ARDS patients {Millar *et al.*, *Lancet* 2(8665), 712-714 (1989)}.
Systemic infusion of recombinant TNF α also resulted in changes typically seen in
ARDS {Ferrai-Baliviera *et al.*, *Arch. Surg.* 124(12), 1400-1405 (1989)}.

25 TNF α appears to be involved in bone resorption diseases, including arthritis.
When activated, leukocytes will produce bone-resorption, an activity to which the
data suggest TNF α contributes. {Bertolini *et al.*, *Nature* 319, 516-518 (1986) and
Johnson *et al.*, *Endocrinology* 124(3), 1424-1427 (1989).} TNF α also has been
shown to stimulate bone resorption and inhibit bone formation *in vitro* and *in vivo*
30 through stimulation of osteoclast formation and activation combined with inhibition
of osteoblast function. Although TNF α may be involved in many bone resorption

diseases, including arthritis, the most compelling link with disease is the association between production of TNF α by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum TNF α levels have been associated with major
5 complication following acute allogenic bone marrow transplants {Holler *et al.*, *Blood*, 75(4), 1011-1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNF α and the most severe complication occurring in malaria patients. Levels of serum TNF α correlated directly with the severity of disease and the
10 prognosis in patients with acute malaria attacks {Grau *et al.*, *N. Engl. J. Med.* 320(24), 1586-1591 (1989)}.

Macrophage-induced angiogenesis TNF α is known to be mediated by TNF α . Leibovich *et al.* {*Nature*, 329, 630-632 (1987)} showed TNF α induces *in vivo* capillary blood vessel formation in the rat cornea and the developing chick
15 chorioallantoic membranes at very low doses and suggest TNF α is a candidate for inducing angiogenesis in inflammation, wound repair, and tumor growth. TNF α production also has been associated with cancerous conditions, particularly induced tumors {Ching *et al.*, *Brit. J. Cancer*, (1955) 72, 339-343, and Koch, *Progress in Medicinal Chemistry*, 22, 166-242 (1985)}.

20 TNF α also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNF α completely blocked the silica-induced lung fibrosis in mice {Pignet *et al.*, *Nature*, 344, 245-247 (1990)}. High levels of TNF α production (in the serum and in isolated macrophages) have
25 been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette *et al.*, *Inflammation* 13(3), 329-339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNF α as compared with macrophages from normal donors {Baughman *et al.*, *J. Lab. Clin. Med.* 115(1), 36-42 (1990)}.

30 TNF α is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder *et al.*, *PNAS* 87, 2643-2646 (1990)}. TNF α also alters the properties of

endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry *et al.*, *J. Cell Biol.* 107, 1269-1277 (1988)}. TNF α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF α -induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro *et al.*, *Am. J. Path.* 135(1), 121-132 (1989)}.

TNF α blockage with monoclonal anti-TNF α antibodies has been shown to be beneficial in rheumatoid arthritis {Elliot *et al.*, *Int. J. Pharmac.* 1995 17(2), 141-145}. High levels of TNF α are associated with Crohn's disease {von Dullemen *et al.*, *Gastroenterology*, 1995 109(1), 129-135} and clinical benefit has been achieved with TNF α antibody treatment.

Moreover, it now is known that TNF α is a potent activator of retrovirus replication including activation of HIV-1. {Duh *et al.*, *Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll *et al.*, *Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto *et al.*, *Blood* 79, 2670 (1990); Clouse *et al.*, *J. Immunol.* 142, 431-438 (1989); Poll *et al.*, *AIDS Res. Hum. Retrovirus*, 191-197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, *i.e.*, HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNF α , are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNF α , in an HIV-

infected individual assists in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, also have been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg *et al.*, *The Immunopathogenesis of HIV Infection*, Advances in Immunology, 57 (1989)}. Cytokines, such as TNF α , have been shown to activate HIV replication in monocytes and/or macrophages {Poli *et al.*, *Proc. Natl. Acad. Sci.*, 87, 782-784 (1990)}, therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression for T cells. Additional studies have identified TNF α as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, *et al.*, *PNAS* 86 2336-2340). This evidence suggests that a reduction of TNF α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF α {Folks *et al.*, *PNAS* 86, 2365-2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNF α 's ability to activate a gene regulatory protein (NF κ B) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn *et al.*, *PNAS* 86, 2336-2340 (1989)}. TNF α in AIDS associated cachexia is suggested by elevated serum TNF α and high levels of spontaneous TNF α production in peripheral blood monocytes from patients {Wright *et al.*, *J. Immunol.* 141(1), 99-104 (1988)}. TNF α has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

The nuclear factor κ B (NF κ B) is a pleiotropic transcriptional activator (Lenardo, *et al.*, *Cell* 1989, 58, 227-29). NF κ B has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNF α and also to be an activator of HIV transcription (Dbaibo, *et al.*, *J. Biol. Chem.* 1993, 17762-66; Duh *et al.*, *Proc. Natl. Acad. Sci.* 1989, 86, 5974-78; Bachelerie *et al.*, *Nature* 1991, 350, 709-12; Boswas *et al.*, *J. Acquired Immune Deficiency Syndrome* 1993, 6, 778-786; Suzuki *et al.*, *Biochem.*

And Biophys. Res. Comm. 1993, 193, 277-83; Suzuki *et al.*, *Biochem. And Biophys. Res Comm.* 1992, 189, 1709-15; Suzuki *et al.*, *Biochem. Mol. Bio. Int.* 1993, 31(4), 693-700; Shakhov *et al.*, *Proc. Natl. Acad. Sci. USA* 1990, 171, 35-47; and Staal *et al.*, *Proc. Natl. Acad. Sci. USA* 1990, 87, 9943-47). Thus, inhibition of NF κ B binding
5 can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds described herein can inhibit the action of NF κ B in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions,
10 septic shock, sepsis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS. TNF α and NF κ B levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNF α and NF κ B.

15 Many cellular functions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). Such cellular functions can contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions (Lowe and Cheng, *Drugs of the Future*, 17(9), 799-807, 1992). It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release
20 of inflammatory mediators, including TNF α and NF κ B. Increased levels of cAMP also leads to the relaxation of airway smooth muscle. Phosphodiesterases control the level of cAMP through hydrolysis and inhibitors of phosphodiesterases have been shown to increase cAMP levels.

Decreasing TNF α levels and/or increasing cAMP levels thus constitutes a valuable
25 therapeutic strategy for the treatment of many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer,
30 autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythematosus, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Prior efforts directed to the suppression of the effects of TNF α have ranged from the utilization of steroids such

as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies {Beutler *et al.*, *Science* 234, 470-474 (1985); WO 92/11383}.

Matrix metalloproteinase (MMP) inhibition has been associated with inhibition of TNF. Mohler *et al.*, *Nature*, 370, 218-220 (1994). MMPs, or matrixins, are a family of secreted and membrane-bound zinc endopeptidases that play a key role in both physiological and pathological tissue degradation. See Yu *et al.*, *Drugs & Aging*, 1997, (3):229-244; Wojtowicz-Praga *et al.*, *Int. New Drugs*, 16:61-75 (1997). These enzymes are capable of degrading the components of the extracellular matrix, including fibrillar and non-fibrillar collagens, fibronectin, laminin, and membrane glycoproteins. Ordinarily, there is a delicate balance between cell division, matrix synthesis, and matrix degradation (under the control of cytokines), growth factors, and cell matrix interactions. Under pathological conditions, however, this balance can be disrupted. Conditions and diseases associated with undesired MMP levels include, but are not limited to, tumor metastasis, invasion, and growth, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, and corneal epidermal or gastric ulceration.

Increased MMP activity has been detected in a wide range of cancers, Denis *et al.*, *Invest. New Drugs*, 15: 175-185 (1987), and as with TNF, MMPs are believed to be involved in the invasive processes of angiogenesis and tumor metastasis.

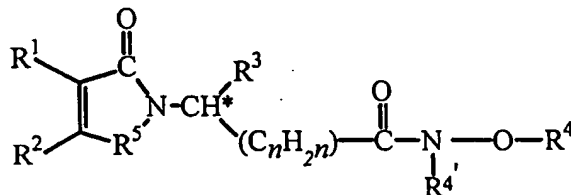
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Detailed Description

The present invention is based on the discovery that certain classes of non-polypeptide compounds more fully described herein decrease the levels of TNF α , increase cAMP levels, and inhibit phosphodiesterase.

In particular, the invention pertains to

(a) compounds of the formula:



I.

5 wherein

each of R¹ and R², when taken independently of each other, is hydrogen, lower alkyl, or R¹ and R², when taken together, together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo;

15 R³ is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, alkylthio of 1 to 10 carbon atoms, benzyloxy, cycloalkoxy of 3 to 6 carbon atoms, C₄-C₆-cycloalkylidenemethyl, C₁-C₁₀-alkylidenemethyl, indanyloxy, and halo;

20 R^4 is hydrogen, alkyl of 1 to 6 carbon atoms, phenyl, or benzyl;

R^{4'} is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is -CH₂-, -CH₂-CO-, -CO-, -SO₂-, -S-, or -NHCO-; and

n has a value of 0, 1, or 2; and

(b) the acid addition salts of said compounds which contain a nitrogen atom
25 capable of being protonated.

Unless otherwise defined, the term alkyl denotes a univalent saturated branched or straight hydrocarbon chain containing from 1 to 8 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl. Alkoxy refers to an alkyl group bound to the remainder of the molecule

through an ethereal oxygen atom. Representative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, and tert-butoxy.

The compounds of Formula I are used, under the supervision of qualified professionals, to inhibit the undesirable effects of $\text{TNF}\alpha$ and inhibit phosphodiesterase. The
5 compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment.

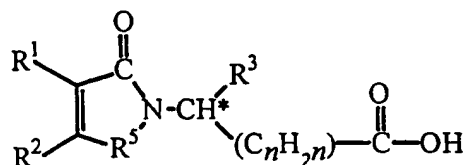
The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive $\text{TNF}\alpha$
10 production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, psoriasis, atopic dermatitis, *etc.*

The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of $\text{TNF}\alpha$ production. $\text{TNF}\alpha$ mediated diseases for treatment, therapeutically or prophylactically, in animals
15 include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

The invention also relates to MMP-inhibiting compounds, compositions thereof, and their use in the treatment of diseases and disorders associated with undesired
20 production or activity of MMPs. These compounds are capable of inhibiting connective tissue breakdown, and are useful in the treatment or prevention of conditions involving tissue breakdown. These include, but are not limited to, tumor metastasis, invasion, and growth, rheumatoid arthritis, osteoarthritis, osteopenias such as osteoporosis, periodontitis, gingivitis, and corneal epidermal or gastric ulceration.

25 The invention thus further comprises MMP-inhibiting compounds of Formula I, and methods of treatment comprising administering an effective amount of a compound according to Formula I.

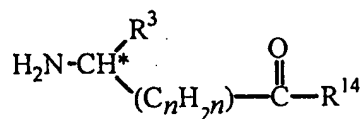
The compounds of Formula I are readily prepared by reacting a carboxylic acid of the formula:



II

- 5 in which each of R^1 , R^2 , R^3 , R^5 , and n are as defined above, with hydroxylamine hydrochloride or alkoxyamine hydrochloride in the presence of a coupling agent. The reaction generally is conducted in an inert solvent such as tetrahydrofuran under an inert atmosphere such as nitrogen. Ambient temperatures can be employed. When the reaction is substantially complete, the products can be readily isolated simply
10 through the addition of water.

The compounds of Formula II which are here utilized as intermediates are described in U.S. Patent No. 5,605,914, the disclosure of which is incorporated herein by reference. Briefly, such intermediates can be prepared through the reaction of an amino acid of the formula:



15

III

in which R^{14} is hydroxy or a protecting group, with an acid anhydride, an N-carbethoxyimide, a dialdehyde, or an *o*-bromo aromatic acid.

- Protecting groups utilized herein denote groups which generally are not found in
20 the final therapeutic compounds but which are intentionally introduced at some stage of the synthesis in order to protect groups which otherwise might be altered in the course of chemical manipulations. Such protecting groups are removed at a later stage of the synthesis and compounds bearing such protecting groups thus are of importance primarily as chemical intermediates (although some derivatives also
25 exhibit biological activity). Accordingly the precise structure of the protecting group is not critical. Numerous reactions for the formation and removal of such protecting groups are described in a number of standard works including, for example,

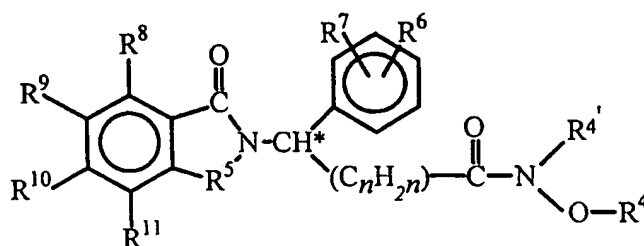
- "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973; Greene, Th. W. "Protective Groups in Organic Synthesis", Wiley, New York, 1981; "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965; "Methoden der organischen Chemie", Houben-Weyl, 4th Edition, Vol.15/I, Georg Thieme Verlag, Stuttgart 1974, the disclosures of which are incorporated herein by reference.

- In any of the foregoing reactions, a nitro compound can be employed with the nitro group being converted to an amino group by catalytic hydrogenation. Alternatively, a protected amino group can be cleaved to yield the corresponding amino compound.
- 10 An amino group can be protected as an amide utilizing an acyl group which is selectively removable under mild conditions, especially benzyloxycarbonyl, formyl, or a lower alkanoyl group which is branched in 1- or α position to the carbonyl group, particularly tertiary alkanoyl such as pivaloyl, a lower alkanoyl group which is substituted in the position α to the carbonyl group, as for example trifluoroacetyl.
- 15 The compounds of Formula I possess at least one center of chirality (designated by "**") and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by
- 20 chromatography using a chiral absorbant. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid or base, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, α -bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then
- 25 freeing one or both of the resolved bases, optionally repeating the process, so as obtain either or both substantially free of the other; *i.e.*, in a form having an optical purity of >95%.

- The present invention also pertains to the physiologically acceptable non-toxic acid addition salts of the compound of Formula I. Such salts include those derived
- 30 from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

The present invention also pertains to the physiologically acceptable non-toxic salts of the compound of Formula I with bases such as the sodium salt, the potassium salt, the aluminum salt, and the like.

A first preferred subgroup encompasses compounds of the formula:



IV.

in which

R^4 is hydrogen or alkyl of 1 to 4 carbon atoms;

$R^{4'}$ is hydrogen or alkyl of 1 to 4 carbon atoms;

R^5 is C=O or CH₂;

each of R^6 and R^7 , independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, bicycloalkyl of 6 to 10 carbon atoms, indanyloxy, C₄-C₆-cycloalkylidenemethyl, C₃-C₁₀-alkylidenemethyl, or halo;

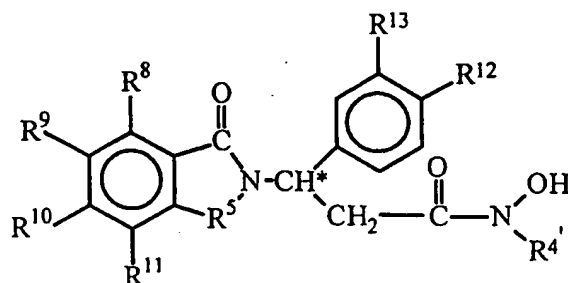
each of R^8 , R^9 , R^{10} , and R^{11} , independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo; and

n has a value of 1.

Among the compounds of Formula IV, those in which each of R^8 , R^9 , R^{10} , and R^{11} is hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and

those in which one of R^8 , R^9 , R^{10} , and R^{11} is amino, hydroxy, or methyl, and the remaining of R^8 , R^9 , R^{10} , and R^{11} , are hydrogen are particularly preferred.

A further preferred subgroup encompasses compounds of the formula:



V.

in which

$R^{4'}$ is hydrogen or alkyl of 1 to 4 carbon atoms;

R^5 is C=O or CH₂;

each of R^{12} and R^{13} , independently of the other alkoxy of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms; C₄-C₆-cycloalkyldenemethyl, C₃-C₁₀-alkyldenemethyl, or indanyloxy; and

each of R^8 , R^9 , R^{10} , and R^{11} , independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo.

Among the compounds of Formula V, those in which each of R^8 , R^9 , R^{10} , and R^{11} is hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms, and those in which one of R^8 , R^9 , R^{10} , and R^{11} is amino or hydroxy and the remaining of R^8 , R^9 , R^{10} , and R^{11} , are hydrogen are particularly preferred.

Particularly preferred compounds include 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisindoliny)propionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindoliny)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-

N-hydroxy-3-phthalimidopropionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindoliny)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide, 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide, N-hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide, 3-(4-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindoliny)propionamide, 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide, and N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide.

Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms containing from 1 to 100 mg of drug per unit dosage. Isotonic saline solutions containing from 20 to 100 mg/mL can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Pharmaceutical compositions thus comprise one or more compounds of Formulas I associated with at least one pharmaceutically acceptable carrier, diluent or excipient. In preparing such compositions, the active ingredients are usually mixed with or diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule or sachet. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. Examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starch, gum acacia, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidinone, cellulose, water, syrup, and methyl cellulose, the formulations can additionally include lubricating agents such as talc, magnesium stearate and mineral oil, wetting agents, emulsifying and suspending agents, preserving agents such as methyl- and propylhydroxybenzoates, sweetening agents or flavoring agents.

The compositions preferably are formulated in unit dosage form, meaning physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient. The compositions can be formulated so as to provide an immediate, sustained or delayed release of active ingredient after administration to the patient by employing procedures well known in the art.

Enzyme-linked immunosorbent assays for TNF α can be performed in a conventional manner. PBMC is isolated from normal donors by Ficoll-Hypaque density centrifugation. Cells are cultured in RPMI supplemented with 10% AB+ serum, 2mM L-glutamine, 100 U/mL penicillin, and 100 mg/mL streptomycin. Drugs are dissolved in dimethylsulfoxide (Sigma Chemical) and further dilutions are done in supplemented RPMI. The final dimethylsulfoxide concentration in the presence or absence of drug in the PBMC suspensions is 0.25 wt %. Drugs are assayed at half-log dilutions starting at 50 mg/mL. Drugs are added to PBMC (10^6 cells/mL) in 96 wells plates one hour before the addition of LPS. PBMC (10^6 cells/mL) in the presence or absence of drug are stimulated by treatment with 1 mg/mL of LPS from *Salmonella minnesota* R595 (List Biological Labs, Campbell, CA). Cells are then incubated at 37° C for 18-20 hours. Supernatants are harvested and assayed immediately for TNF α levels or kept frozen at -70°C (for not more than 4 days) until assayed. The concentration of TNF α in the supernatant is determined by human TNF α ELISA kits (ENDOGEN, Boston, MA) according to the manufacturer's directions.

Phosphodiesterase can be determined in conventional models. For example, using the method of Hill and Mitchell, U937 cells of the human promonocytic cell line are grown to 1×10^6 cells /mL and collected by centrifugation. A cell pellet of 1×10^9 cells is washed in phosphate buffered saline and then frozen at -70°C for later purification or immediately lysed in cold homogenization buffer (20mM Tris-HCl, pH 7.1, 3 mM 2-mercaptoethanol, 1 mM magnesium chloride, 0.1 mM ethylene glycol-bis-(β -aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), 1 μ M phenylmethylsulfonyl fluoride (PMSF), and 1 μ g/mL leupeptin). Cells are homogenized with 20 strokes in a Dounce homogenizer and supernatant containing the cytosolic fraction are obtained by centrifugation. The supernatant then is loaded onto a Sephacryl S-200 column equilibrated in homogenization buffer. Phosphodiesterase is eluted in

homogenization buffer at a rate of approximately 0.5 mL/min and fractions are assayed for phosphodiesterase activity +/- rolipram. Fractions containing phosphodiesterase activity(rolipram sensitive) are pooled and aliquoted for later use.

The phosphodiesterase assay is carried out based on procedure described by Hill and Mitchell. The assay is carried out in a total volume of 100 μ l containing various concentration of Celgene compounds, 50mM Tris-HCl, pH 7.5, 5 mM magnesium chloride and 1 μ M cAMP of which 1% was 3 H cAMP. Reactions are incubated at 30°C for 30 minutes and terminated by boiling for 2 minutes. The amount of phosphodiesterase IV containing extract used for these experiments is predetermined such that reactions are within the linear range and consumed less than 15% of the total substrate. Following termination of reaction, samples are chilled at 4°C and then treated with 10 μ l 10 mg/mL snake venom for 15 min at 30°C. Unused substrate then is removed by adding 200 μ l of a quaternary ammonium ion exchange resin (AG1-X8, BioRad) for 15 minutes. Samples then are spun at 3000 rpm, 5 min and 50 μ l of the aqueous phase are taken for counting. Each data point is carried out in duplicate and activity is expressed as percentage of control. The IC₅₀ of the compound then is determined from dose response curves of a minimum of three independent experiments.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

EXAMPLE 1

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide

A mixture of 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindoliny)propanoic acid (15.0 g, 42.7 mmol) and N,N'-carbonyldiimidazole (7.27 g, 44.8 mmol) in tetrahydrofuran (50 mL) under nitrogen was stirred at room temperature for 2 hours. To the resulting solution was added hydroxylamine hydrochloride (3.86 g, 55.5 mmol). The resulting suspension was stirred for 18 hours. To the suspension was added water (150 mL) and stirring was continued for 1 hour. The suspension was filtered, the solid was washed with water (5 X 30 mL) and ether (2 X 20 mL), and then was dried in a vacuum oven overnight (60 °C, < 1 torr) to give 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide as a white solid

(13.0 g, 82% yield): mp, 167-168 °C; ¹H NMR (DMSO-d₆) δ 1.29 (t, *J* = 6.9 Hz, 3H, CH₃) 2.81-2.86 (m, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.96-4.04 (m, 2H, CH₂), 4.13 (d, *J* = 17.5 Hz, 1H, CHH), 4.54 (d, *J* = 17.5 Hz, 1H, NCHH), 5.73 (t, *J* = 7.9 Hz, 1H, NCH), 6.84-6.92 (m, 3H, Ar), 7.43 -7.68 (m, 4H, Ar), 8.83 (br.s, 1H, OH), 10.61 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.68, 35.04, 46.22, 51.20, 55.44, 63.73, 111.85, 112.19, 119.21, 122.78, 123.43, 127.83, 131.29, 131.85, 132.27, 141.67, 147.85, 148.42, 165.99, 166.82. Anal. Calcd for C₂₀H₂₂N₂O₅: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.73; H, 6.17; N, 7.36.

In a similar fashion, 3-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-hydroxy-3-(4-methylphthalimido)propionamide was prepared from 3-(3-cyclopentyloxy-4-methoxyphenyl)-*N*-hydroxy-3-(4-methylphthalimido)propanoic acid (2.0 g, 4.7 mmol), carbonyl diimidazole (842 mg, 5.19 mmol) and hydroxylamine hydrochloride (426 mg, 6.13 mmol) in tetrahydrofuran (10 mL). The product is a white solid (1.34 g, 65% yield): mp, 112.0-116.0 °C; ¹H NMR (DMSO-d₆) δ 1.56-1.87 (m, 8H, C₅H₈), 2.47 (s, 3H, CH₃), 3.09 (d, *J* = 7.8 Hz, 2H, CH₂), 3.70 (s, 3H, CH₃), 4.71-4.74 (m, 1H, OCH), 5.65 (t, *J* = 7.8 Hz, 1H, NCH), 6.88 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.61-7.76 (m, 3H, Ar), 8.79 (br s, 1H, OH), 10.59 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 21.34, 23.53, 32.19, 34.29, 50.12, 55.54, 79.56, 112.06, 114.10, 119.65, 123.05, 123.53, 128.62, 131.27, 131.60, 134.92, 145.58, 146.72, 149.13, 166.03, 167.64, 167.75; Anal Calcd for C₂₄H₂₆N₂O₆ · 1.2 H₂O: C, 62.65; H, 6.22; N, 6.09. Found: C, 62.56; H, 6.12; N, 5.87.

EXAMPLE 2

3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(4-methylphthalimido)propionamide

A. A stirred solution of 3-amino-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (3.00 g, 12.5 mmol) and 4-methylphthalic anhydride (2.13g, 12.5 mmol, 95%) in acetic acid was heated to reflux under nitrogen for 18 hours. The mixture was allowed to cool to room temperature. The solvent was removed *in vacuo* to give an oil. The resulting oil was stirred with ethyl acetate (10 mL), hexane (10 mL) and water (30 mL) for 30 minutes. The resulting suspension was filtered. The solid was washed with water (3 x 10 mL) and hexane (3 x 10 mL), and then was dried in a vacuum oven overnight (60 °C, < 1 torr) to give 3-(3-ethoxy-4-methoxyphenyl)-3-(4-methylphthalimido)propanoic acid as a white solid (3.4 g, 71% yield): mp, 134.0-136.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 6.9 Hz, 3H, CH₃), 2.47 (s, 3H, CH₃), 3.23 (dd, *J* = 6.7, 16.5 Hz, 1H, CHH), 3.50 (dd, *J* = 9.2, 16.5 Hz, 1H, CHH), 3.72 (s,

3H, CH₃), 3.97 (q, *J* = 6.9 Hz, 2H, CH₂), 5.58 (dd, *J* = 6.7, 9.1 Hz, 1H, NCH), 6.90-6.95 (m, 2H, Ar), 7.01 (br s, 1H, Ar), 7.61-7.76 (m, 3H, Ar), 12.4 (br s, 1H, OH); ¹³C NMR (DMSO-d₆) δ 14.65, 21.32, 36.09, 50.04, 55.45, 63.72, 111.79, 112.15, 119.29, 123.08, 123.58, 128.51, 131.35, 131.49, 134.95, 145.63, 147.75, 148.53, 167.67, 167.78, 171.72; Anal Calcd for C₂₁H₂₁NO₆: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.46; H, 5.57; N, 3.31.

B. 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(4-methyl-phthalimido)propanoic acid (2.40 g, 6.26 mmol), N,N'-carbonyldiimidazole (1.12 g, 6.91 mmol) and hydroxylamine hydrochloride (530 mg, 7.62 mmol) in tetrahydrofuran (8 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide as a white solid (2.19 g, 88% yield): mp, 180.0-181.5 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 6.9 Hz, 3H, CH₃), 2.49 (s, 3H, CH₃), 3.09 (d, *J* = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.97 (q, *J* = 7.0 Hz, 2H, CH₂), 5.65 (t, *J* = 7.9 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.61-7.74 (m, 3H, Ar), 8.78 (br s, 1H, OH), 10.57 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.67, 21.33, 34.31, 50.14, 55.45, 63.72, 111.75, 112.33, 119.61, 123.03, 123.52, 128.63, 131.32, 131.61, 134.88, 145.54, 147.67, 148.52, 166.02, 167.62, 167.73; Anal Calcd for C₂₁H₂₂N₂O₆: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.29; H, 5.69; N, 6.86.

EXAMPLE 3

3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide

A. A mixture of 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propanoic acid (3.00 g, 10.8 mmol) and sodium carbonate (1.20 g, 11.3 mmol) in acetonitrile (30 mL) and water (30 mL) under nitrogen was stirred at room temperature for 15 minutes. To the resulting solution was added N-ethoxycarbonyl phthalimide (2.36 g, 10.8 mmol). The resulting mixture was stirred at room temperature for 18 hours. Most of solvent was removed *in vacuo*. To the solution was added hydrochloric acid (6N) until the pH of solution < 1 to give a suspension and stirring was continued for 1 hour. The suspension was filtered, the solid was washed with water (2 X 10 mL), and then was dried in a vacuum oven overnight (60 °C, < 1 torr) to afford 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phthalimidopropionamide as a white solid (3.0 g, 68% yield): mp, 168.0-169.0 °C; ¹H NMR (DMSO-d₆) δ 1.55-1.88 (m, 8H, C₅H₈), 3.27 (dd, *J* = 6.9, 16.5 Hz, 1H, CHH), 3.51 (dd, *J* = 8.9, 16.5 Hz, 1H, CHH), 3.71 (s, 3H, CH₃), 4.71-4.75 (m, 1H, CH), 5.61 (dd, *J* = 6.9, 8.8 Hz, 1H, NCH), 6.87-6.95 (m,

2H, Ar), 7.03 (br s, 1H, Ar), 7.81-7.91 (m, 4H, Ar), 12.4 (br s, 1H, OH); ^{13}C NMR (DMSO- d_6) δ 23.51, 32.14, 32.17, 36.07, 50.08, 55.52, 79.57, 112.15, 113.97, 119.39, 123.17, 131.09, 131.19, 134.66, 146.77, 149.16, 167.67, 171.72; Anal Calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.21; H, 5.46; N, 3.45.

- 5 B. 3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide was prepared by the procedure of Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-phthalimidopropanoic acid (1.50 g, 3.67 mmol), N,N'-carbonyldiimidazole (653 mg, 4.03 mmol) and hydroxylamine hydrochloride (308 mg, 4.43 mmol) in tetrahydrofuran (5 mL) to afford 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide as a white solid (1.45 g, 93% yield): mp, 169.0-171.0 $^{\circ}\text{C}$; ^1H NMR (DMSO- d_6) δ 1.54-1.85 (m, 8H, C_5H_8), 3.09 (d, $J = 7.9$ Hz, 2H, CH_2), 3.69 (s, 3H, CH_3), 4.70-4.72 (m, 1H, CH), 5.67 (t, $J = 7.9$ Hz, 1H, NCH), 6.87 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.79-7.87 (m, 4H, Ar), 8.78 (br s, 1H, OH), 10.58 (1H, NH); ^{13}C NMR (DMSO- d_6) δ 23.51, 32.17, 34.23, 50.19, 55.53, 79.57, 112.08, 114.16, 119.69, 123.11, 131.16, 131.20, 134.59, 146.73, 149.17, 166.01, 167.63; Anal Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_6$: C, 65.08; H, 5.70; N, 6.60. Found: C, 64.73; H, 5.60; N, 6.53.
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EXAMPLE 4

N-Hydroxy-N-methyl-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide

- 20 *N*-Hydroxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propanoic acid (1.0 g, 2.8 mmol), carbonyldiimidazole (500 mg, 3.1 mmol) and *N*-methyl-hydroxylamine hydrochloride (300 mg, 3.5 mmol) in tetrahydrofuran (10 mL) to afford *N*-hydroxy-*N*-methyl-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide as a white solid (650 mg, 61% yield): mp, 122.0-124.5 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.43 (t, $J = 7.0$ Hz, 3H, CH_3), 3.14 (s, 3H, NCH_3), 3.37-3.48 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.02 (q, $J = 7.0$ Hz, 2H, CH_2), 4.11 (d, $J = 17.2$ Hz, NCHH), 4.51 (d, $J = 17.2$ Hz, 1H, NCHH), 5.95 (dd, $J = 6.5$, 10.9 Hz, 1H, NCH), 6.83-6.97 (m, 3H, Ar), 7.34-7.55 (m, 3H, Ar), 7.81 (d, $J = 7.1$ Hz, 1H, Ar), 9.44 (br s, 1H, OH); ^{13}C NMR (DMSO- d_6) δ 14.71, 36.04, 38.11, 48.14, 52.36, 55.95, 64.52, 111.42, 112.42, 119.45, 122.95, 123.63, 128.06, 130.57,
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131.88, 141.72, 148.65, 149.18, 170.00, 170.17; Anal Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.56; H, 6.26; N, 7.09.

EXAMPLE 5

5 *3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)-propionamide*

3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propanoic acid (2.0 g, 4.7 mmol), carbonyldiimidazole (842 mg, 5.19 mmol) and hydroxylamine hydrochloride (426 mg, 6.13 mmol) in tetrahydrofuran (10 mL) to afford 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide as a white solid (1.34 g, 65% yield): mp, 112.0-116.0 °C; 1H NMR (DMSO- d_6) δ 1.56-1.87 (m, 8H, C_5H_8), 2.47 (s, 3H, CH_3), 3.09 (d, $J = 7.8$ Hz, 2H, CH_2), 3.70 (s, 3H, CH_3), 4.71-4.74 (m, 1H, OCH), 5.65 (t, $J = 7.8$ Hz, 1H, NCH), 6.88 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.61-7.76 (m, 3H, Ar), 8.79 (br s, 1H, OH), 10.59 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 21.34, 23.53, 32.19, 34.29, 50.12, 55.54, 79.56, 112.06, 114.10, 119.65, 123.05, 123.53, 128.62, 131.27, 131.60, 134.92, 145.58, 146.72, 149.13, 166.03, 167.64, 167.75; Anal Calcd for $C_{24}H_{26}N_2O_6 \cdot 1.2 H_2O$: C, 62.65; H, 6.22; N, 6.09. Found: C, 62.56; H, 6.12; N, 5.87.

EXAMPLE 6

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide

A. 3-(3-Ethoxy-4-methoxyphenyl)-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propanoic acid was prepared according to Example 2A from 3-amino-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (3.00 g, 12.5 mmol), 2,3-naphthalene dicarboxylic anhydride (2.59 g, 12.5 mmol) in acetic acid (20 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propanoic acid as an off-white solid (4.9 g, 93% yield): mp, 193.0-194.0 °C; 1H NMR (DMSO- d_6) δ 1.32 (t, $J = 6.9$ Hz, 3H, CH_3), 3.34 (dd, $J = 7.1, 16$ Hz, 1H, CHH), 3.57 (dd, $J = 8.9, 16$ Hz, 1H, CHH), 3.74 (s, 3H, CH_3), 4.02 (q, $J = 6.9$ Hz, 2H, CH_2), 5.71 (dd, $J = 7, 8$ Hz, 1H, NCH), 6.91-6.98 (m, 2H, Ar), 7.09 (br s, 1H, Ar), 7.74-7.78 (m, 2H, Ar), 8.23-8.27 (m, 2H, Ar), 8.50 (br s, 2H, Ar), 12.5 (br s, 1H, OH); ^{13}C NMR (DMSO- d_6) δ 14.62, 36.03, 50.28, 55.43, 63.71, 111.79, 112.28,

119.45, 124.55, 126.87, 129.27, 130.24, 131.24, 135.03, 147.74, 148.57, 167.29, 171.75; Anal Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.59; H, 5.25; N, 3.17.

B. 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]-isoindol-2-yl)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propanoic acid (2.00 g, 4.77 mmol), N,N'-carbonyldiimidazole (889 mg, 5.48 mmol) and hydroxylamine hydrochloride (419 mg, 6.03 mmol) in tetrahydrofuran (8 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide as an off-white solid (1.6 g, 77% yield): mp, 197.0-199.0 °C; 1H NMR (DMSO- d_6) δ 1.33 (t, J = 7.0 Hz, 3H, CH_3), 3.11-3.28 (m, 2H, CH_2), 3.73 (s, 3H, CH_3), 4.00 (q, J = 7.0 Hz, 2H, CH_2), 5.79 (t, J = 7.8 Hz, 1H, NCH), 6.87-7.09 (m, 2H, Ar), 7.10 (br s, 1H, Ar), 7.74-7.78 (m, 2H, Ar), 8.23-8.27 (m, 2H, Ar), 8.49 (br s, 1H, Ar), 8.85 (br s, 1H, OH), 10.66 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 14.69, 34.27, 50.42, 55.45, 63.73, 111.73, 112.45, 119.82, 124.50, 127.04, 129.28, 130.26, 131.20, 135.05, 147.69, 148.58, 166.07, 167.30; Anal Calcd for $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.22; H, 5.24; N, 6.08.

EXAMPLE 7

3-(3-Ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisindolinyl)propionamide

A mixture of 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propanoic acid (500 mg, 1.41 mmol) and N,N'-carbonyldiimidazole (250 mg, 1.54 mmol) in methylene chloride (30 mL) under nitrogen was stirred at room temperature for 30 minutes. To the solution was added O-methyl hydroxylamine hydrochloride (175 mg, 2.09 mmol) followed by the addition of 1-methyl piperidine (0.26 mL, 2.14 mmol). The mixture was stirred at room temperature for 2 hours and then was heated to reflux for 14 hours. The cooled reaction mixture was washed with hydrochloric acid (1N, 25 mL), saturated sodium bicarbonate (25 mL), brine (25 mL), and then dried over sodium carbonate and sodium sulfate. Removal of solvent *in vacuo* gave a solid which was stirred with ether (10 mL) for 30 minutes. This suspension was filtered and the solid was washed with ether (2 X 10 mL) to give 3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisindolinyl)-propionamide as a white solid (360 mg, 67% yield): mp, 138.0-139.5 °C; 1H NMR ($CDCl_3$) δ 1.41 (t, J = 6.9 Hz, 3H, CH_3), 2.95 (dd, J = 4.6, 14.5 Hz, 1H, CHH), 3.53 (dd, J = 11.2, 14.5 Hz, 1H, CHH), 3.62 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 4.02 (q, J = 6.9 Hz, 2H, CH_2), 4.23 (d, J = 17.1 Hz, 1H, NCHH), 4.46 (d, J = 17 Hz, 1H, NCHH), 5.49 (dd, J = 4.4, 10.3 Hz,

1H, NCH), 6.78-6.99 (m, 3H, Ar), 7.27-7.51 (m, 3H, Ar), 7.78 (dd, $J = 7.4$ Hz, 1H, Ar), 10.08 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 14.66, 37.52, 49.48, 54.94, 5.91, 64.01, 64.41, 111.37, 112.12, 119.26, 122.75, 123.54, 128.04, 131.38, 131.68, 132.58, 141.44, 148.56, 149.15, 167.81, 169.47. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.23; H, 6.52; N, 6.88.

EXAMPLE 8

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-phthalimido-propanoic acid (869 mg, 2.36 mmol), N,N'-carbonyldiimidazole (410 mg, 2.53 mmol) and O-benzylhydroxylamine hydrochloride (444 mg, 2.78 mmol) in tetrahydrofuran (6 mL) to afford N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide as a white solid (1.05 g, 94% yield): mp, 165.0-166.0 °C; ^1H NMR (CDCl_3) δ 1.44 (t, $J = 7.0$ Hz, 3H, CH_3), 2.95 (dd, $J = 5.8, 14.0$ Hz, 1H, CHH), 3.49 (t, $J = 12.1$ Hz, 1H, CHH), 3.83 (s, 3H, CH_3), 4.07 (q, $J = 7.0$ Hz, 2H, CH_2), 4.77 (br s, 2H, PhCH_2), 5.83 (dd, $J = 6.0, 10.0$ Hz, 1H, NCH), 6.79 (d, $J = 8.0$ Hz, 1H, Ar), 7.06-7.09 (m, 2H, Ar), 7.25-7.85 (m, 5H, Ar), 7.66-7.71 & 7.74-7.79 (2ms, 4H, Ar), 8.34 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 14.68, 35.66, 51.54, 55.88, 64.34, 78.13, 111.32, 12.52, 120.08, 123.29, 128.52, 128.67, 129.06, 131.26, 131.76, 133.98, 134.98, 148.31, 149.15, 167.38, 168.26. Anal. Calcd for $\text{C}_{27}\text{H}_{26}\text{N}_2\text{O}_6$: C, 68.34; H, 5.52; N, 5.90. Found: C, 68.36; H, 5.47; N, 5.74.

EXAMPLE 9

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propanoic acid (1.30 g, 3.14 mmol), N,N'-carbonyldiimidazole (533 mg, 3.28 mmol) and O-benzylhydroxylamine hydrochloride (550 mg, 3.45 mmol) in tetrahydrofuran (10 mL) to afford N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide as a yellow solid (1.4 g, 86% yield): mp, 137.0-139.0 °C; ^1H NMR ($\text{DMSO}-d_6$) δ 1.30 (t, $J = 6.8$ Hz, 3H, CH_3), 3.05-3.16 (m, 2H, CH_2), 3.72 (s, 3H, CH_3), 4.09 (q, $J = 6.8$ Hz, 2H, CH_2), 4.64 (s, 2H, PhCH_2), 5.68 (t, $J = 7.8$ Hz, 1H, NCH), 6.87-7.02 (m, 3H, Ar), 7.23-7.41 (m, 5H, Ar), 8.11 (d, $J = 8.1$ Hz, 1H, Ar), 8.48 (s, 1H, Ar), 8.62 (dd, $J = 1.8, 8.2$ Hz, 1H, Ar), 11.24 (br s, 1H, NH); ^{13}C NMR ($\text{DMSO}-d_6$) δ 14.64, 34.17, 50.76, 55.45, 63.71, 76.67,

111.68, 112.37, 118.02, 119.76, 124.70, 128.16, 128.62, 129.75, 130.42, 132.52, 135.74, 135.79, 147.73, 148.69, 151.50, 165.73, 165.99, 166.17. Anal. Calcd for $C_{27}H_{25}N_3O_8$: C, 62.42; H, 4.85; N, 8.09. Found: C, 62.34; H, 4.71; N, 8.05.

EXAMPLE 10

5 *N*-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propanoic acid (1.78 g, 5.00 mmol), *N,N'*-carbonyldiimidazole (850 mg, 5.24 mmol) and *O*-benzylhydroxylamine hydrochloride (940 mg, 5.89 mmol) in tetrahydrofuran (10 mL) to afford *N*-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide as a white solid (1.73 g, 75% yield): mp, 132.0-133.0 °C; 1H NMR (DMSO- d_6) δ 1.29 (t, J = 6.9 Hz, 3H, CH_3), 2.83 (d, J = 7.8 Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 3.93-4.02 (m, 2H, CH_2), 4.09 (d, J = 17.5 Hz, 1H, NCHH), 4.51 (d, J = 17.5 Hz, 1H, NCHH), 4.59 (d, J = 11.3 Hz, 1H, PhCHH), 4.66 (d, J = 11.2 Hz, 1H, PhCHH), 5.74 (t, J = 7.8 Hz, 1H, NCH), 6.83-6.93 (m, 3H, Ar), 7.21-7.29 & 7.45-7.59 (m, 8H, Ar), 7.68 (d, J = 7.4 Hz, 1H, Ar), 11.17 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 14.66, 35.08, 46.18, 51.29, 55.43, 63.71, 76.69, 111.82, 112.11, 119.25, 122.82, 123.44, 127.85, 128.17, 128.75, 131.31, 131.61, 132.17, 135.86, 141.68, 147.88, 148.45, 166.26, 166.88. Anal. Calcd for $C_{27}H_{28}N_2O_5$: C, 70.42; H, 6.13; N, 6.08. Found: C, 70.31; H, 6.07; N, 5.88.

EXAMPLE 11

3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-phthalimidopropionamide

3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-phthalimidopropionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropanoic acid (1.00 g, 2.71 mmol), *N,N'*-carbonyldiimidazole (461 mg, 2.84 mmol) and hydroxylamine hydrochloride (208 mg, 2.99 mmol) in tetrahydrofuran (6 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-phthalimidopropionamide as a white solid (800 mg, 77% yield): mp, 163.0-165.0 °C; 1H NMR (DMSO- d_6) δ 1.31 (t, J = 6.9 Hz, 3H, CH_3), 3.11 (d, J = 7.9 Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 3.97 (q, J = 6.9 Hz, 2H, CH_2), 5.67 (t, J = 7.8 Hz, 1H, NCH), 6.90 (br s, 2H, Ar), 7.02 (br s, 1H, Ar), 7.86 (br s, 4H, Ar), 8.79 (br s, 1H, OH), 10.59 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 14.67, 34.22, 50.18, 55.44, 63.71, 111.73, 112.36, 119.65, 123.11, 131.18, 131.21, 134.56, 147.67, 148.53, 165.97, 167.61.

Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.43; H, 5.04; N, 7.20.

EXAMPLE 12

N-Hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide

5 N-Hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide was prepared by the procedure of Example 1 from 3-(3,4-dimethoxyphenyl)-3-phthalimidopropanoic acid (1.82 g, 5.12 mmol), N,N'-carbonyldiimidazole (870 mg, 5.39 mmol) and hydroxylamine hydrochloride (391 mg, 5.63 mmol) in tetrahydrofuran (8 mL) to afford N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide as a white solid (1.52 g, 80% yield): mp, 186.5-188.0 °C; 1H NMR (DMSO- d_6) δ 3.12 (d, J = 7.8 Hz, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.69 (t, J = 7.8 Hz, 1H, NCH), 6.91-6.92 (m, 2H, Ar), 7.03 (br s, 1H, Ar), 7.85 (br s, 4H, Ar), 8.82 (s, 1H, OH), 10.62 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 34.33, 50.25, 55.52, 111.27, 111.67, 119.65, 123.17, 131.26, 134.63, 148.41, 148.56, 166.07, 167.69. Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.29; H, 4.72; N, 7.47.

EXAMPLE 13

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitro-phthalimido)propanoic acid (3.64 g, 8.86 mmol), N,N'-carbonyldiimidazole (1.50 g, 9.25 mmol) and hydroxylamine hydrochloride (672 mg, 9.67 mmol) in tetrahydrofuran (20 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide as a yellow solid (2.92 g, 77% yield): mp, 162.5-163.5 °C; 1H NMR (DMSO- d_6) δ 1.31 (t, J = 6.9 Hz, 3H, CH_3), 3.02 (dd, J = 7.5, 14.8 Hz, 1H, CHH), 3.17 (dd, J = 8.3, 14.8 Hz, 1H, CHH), 3.72 (s, 3H, CH_3), 4.00 (q, J = 6.9 Hz, 2H, CH_2), 5.68 (t, J = 7.7 Hz, 1H, NCH), 6.87-6.96 (m, 2H, Ar), 7.01 (br s, 1H, Ar), 8.05 (t, J = 7.7 Hz, 1H, Ar), 8.15 (d, J = 7.0 Hz, 1H, Ar), 8.27 (d, J = 7.8 Hz, 1H, Ar), 8.82 (s, 1H, OH), 10.62 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 14.66, 33.92, 50.59, 55.46, 63.74, 111.69, 112.59, 119.89, 122.48, 126.91, 128.43, 130.42, 133.13, 136.35, 144.33, 147.67, 148.67, 162.99, 165.70, 165.87. Anal. Calcd for $C_{20}H_{19}N_3O_8$ + 0.4 mole ethyl acetate: C, 55.83; H, 4.86; N, 8.96. Found: C, 55.86; H, 4.94; N, 8.73.

EXAMPLE 14***N-Hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide***

N-Hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide was prepared by the procedure of Example 1 from 3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropanoic acid (2.0 g, 5.2 mmol), carbonyldiimidazole (1.02 g, 6.29 mmol), and hydroxylamine hydrochloride (481 mg, 6.92 mmol) in tetrahydrofuran (10 mL) to afford N-hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide as a white solid (1.42 g, 68% yield): mp, 119.0-121.0 °C; ¹H NMR (DMSO-d₆) δ 1.24 (d, J = 6.0 Hz, 3H, CH₃), 1.243 (d, J = 6.0 Hz, 3H, CH₃), 3.12 (d, J = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 4.45-4.51 (m, 1H, CH), 5.68 (t, J = 7.9 Hz, 1H, NCH), 6.91 (br s, 2H, Ar), 7.05 (br s, 1H, Ar), 7.84-7.86 (m, 4H, Ar), 8.79 (br s, 1H, OH), 10.60 (1H, NH); ¹³C NMR (DMSO-d₆) δ 21.80, 21.88, 34.19, 50.13, 55.49, 70.44, 112.18, 114.97, 120.12, 123.11, 131.13, 131.21, 134.59, 146.37, 149.51, 165.99, 167.62; Anal Calcd for C₂₁H₂₂N₂O₆ 0.9 H₂O: C, 60.83; H, 5.79; N, 6.76. Found: C, 60.83; H, 5.73; N, 6.56; H₂O, 4.02.

EXAMPLE 15***3-(3-Ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide***

3-(3-Ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)propanoic acid (580 mg, 1.43 mmol), carbonyldiimidazole (255 mg, 1.57 mmol) and hydroxylamine hydrochloride (120 mg, 1.73 mmol) in tetrahydrofuran (8 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide as a white solid (340 mg, 57% yield): mp, 171.0-172.0 °C; ¹H NMR (DMSO-d₆) δ 1.32 (t, J = 6.9 Hz, 3H, CH₃), 3.03 (dd, J = 7.9, 14.8 Hz, 1H, CHH), 3.16 (dd, J = 8.1, 14.9 Hz, 1H, CHH), 3.71 (s, 3H, CH₃), 3.91 (q, J = 6.9 Hz, 2H, CH₂), 5.62 (t, J = 7.8 Hz, 1H, NCH), 6.878-6.95 (m, 2H, Ar), 6.99 (br s, 1H, Ar), 7.74 (t, J_{H-F} = 5.8 Hz, 2H, Ar), 8.81 (br s, 1H, OH), 10.61 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.64, 33.88, 50.29, 55.44, 63.71, 111.64, 112.44, 118.02 (t, J_{C-F} = 9.2 Hz), 119.77, 125.47 (t, J_{C-F} = 15 Hz), 130.42, 147.65, 148.59, 152.93 (dd, J_{C-F} = 4.2, 261 Hz), 163.49, 165.84; Anal Calcd for C₂₀H₁₈N₂O₆F₂: C, 57.14; H, 4.32; N, 6.66. Found: C, 56.93; H, 4.37; N, 6.31.

EXAMPLE 16

3-(4-Aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide

A mixture of N-Benzoyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(4-nitrophthalimido)-propionamide (2.3 g, 4.42 mmol) and Pd(OH)₂/C (600 mg) in ethyl acetate/methanol/tetrahydrofuran (150 mL each) was shaken under hydrogen. After 24 hours the suspension was filtered through a pad of Celite, and then was washed with methanol (30 mL) and methylene chloride (30 mL). The filtrate was concentrated *in vacuo* to give an oil. The oil was stirred with ethyl acetate (10 mL) to afford 3-(4-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide as a yellow solid (1.8 g, 100% yield): mp, 193.0-195.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 6.9 Hz, 3H, CH₃), 3.05 (d, *J* = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.96 (q, *J* = 7.0 Hz, 2H, CH₂), 5.57 (t, *J* = 7.9 Hz, 1H, NCH), 6.47 (br s, 2H, NH₂), 6.77 (dd, *J* = 2.0, 8.3 Hz, 1H, Ar), 6.83-6.88 (m, 3H, Ar), 6.99 (br s, 1H, Ar), 7.45 (d, *J* = 8.3 Hz, 1H, Ar), 8.78 (br s, 1H, OH), 10.55 (1H, NH); ¹³C NMR (DMSO-d₆) δ 14.69, 34.51, 49.75, 55.45, 63.73, 106.82, 111.74, 112.38, 116.32, 116.73, 119.60, 124.89, 131.85, 134.18, 147.62, 148.42, 155.00, 166.111, 167.70, 168.00; Anal Calcd for C₂₀H₂₁N₃O₆: C, 60.14; H, 5.30; N, 10.52. -Found: C, 60.00; H, 5.34; N, 10.30.

EXAMPLE 17

N-Hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide

N-Hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide was prepared by the procedure of Example 1 from 3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propanoic acid (5.00 g, 14.7 mmol), carbonyldiimidazole (2.49 g, 15.4 mmol) and hydroxylamine hydrochloride (1.30 g, 19.1 mmol) in tetrahydrofuran (15 mL) to afford N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide as a white solid (4.1 g, 79% yield): mp, 188.5-189.5 °C; ¹H NMR (DMSO-d₆) δ 2.82-2.87 (m, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.74 (s, 3H, CH₃), 4.15 (d, *J* = 17.5 Hz, NCHH), 4.63 (d, *J* = 17.5 Hz, 1H, NCHH), 5.74 (t, *J* = 7.7 Hz, 1H, NCH), 6.85-6.93 (m, 3H, Ar), 7.45-7.69 (m, 4H, Ar), 8.83 (br s, 1H, OH), 10.60 (1H, NH); ¹³C NMR (DMSO-d₆) δ 35.11, 46.26, 51.25, 55.50, 111.09, 111.76, 119.19, 122.79, 123.43, 127.84, 131.29, 131.91, 132.27, 141.68, 148.27, 148.69, 166.03, 166.84; Anal Calcd for C₁₉H₂₀N₂O₅: C, 64.04; H, 5.66; N, 7.86. -Found: C, 64.08; H, 5.55; N, 7.86.

EXAMPLE 18***3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide***

3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propion-
5 amide was prepared by the procedure of Example 1 from 3-(3-cyclopentyloxy-4-methoxyphenyl)-3-(1-oxoisindoliny)propanoic acid (1.00 g, 2.53 mmol), carbonyl-diimidazole (430 mg, 2.66 mmol) and hydroxylamine hydrochloride (230 mg, 3.29 mmol) in tetrahydrofuran (5 mL) to afford 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindoliny)propionamide as a white solid (950 mg, 91% yield):
10 mp, 183.0-184.5 °C; ¹H NMR (DMSO-d₆) δ 1.54-1.82 (m, 8H, C₅H₈), 2.82-2.86 (m, 2H, CH₂), 3.70 (s, 3H, CH₃), 4.13 (d, J = 17.5 Hz, NCHH), 4.55 (d, J = 17.5 Hz, 1H, NCHH), 4.73 (m, 1H, CH), 5.74 (t, J = 7.6 Hz, 1H, NCH), 6.85-6.93 (m, 3H, Ar), 7.47-7.70 (m, 4H, Ar), 8.84 (br s, 1H, OH), 10.60 (1H, NH); ¹³C NMR (DMSO-d₆) δ 23.50, 32.11, 32.18, 46.20, 51.17, 55.53, 79.52, 112.21, 114.00, 119.14, 122.78,
15 123.43, 127.85, 131.31, 131.86, 132.27, 141.65, 146.87, 149.07, 166.04, 166.91; Anal Calcd for C₂₃H₂₆N₂O₅·0.7 H₂O: C, 65.30; H, 6.53; N, 6.62. Found: C, 65.59; H, 6.38; N, 6.65; H₂O, 2.94.

EXAMPLE 19***N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(4-nitrophthalimido)propionamide***

N-Benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(4-nitrophthalimido)propionamide
20 was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(4-nitrophthalimido)propanoic acid (2.84 g, 6.85 mmol), carbonyldiimidazole (1.22 g, 7.52 mmol) and O-benzylhydroxylamine hydrochloride (1.32 g, 8.27 mmol) in tetrahydrofuran (15 mL) to afford N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(4-nitrophthalimido)propionamide as a yellow solid (2.1 g, 59% yield): mp, 159.0-161.0 °C; ¹H NMR (DMSO-d₆) δ 1.30 (t, J = 6.9 Hz, 3H, CH₃), 3.03 (dd, J = 7.7, 14.8 Hz, 1H, CHH), 3.15 (dd, J = 8.0, 14.9 Hz, 1H, CHH), 3.72 (s, 3H, CH₃), 3.96 (q, J = 6.9 Hz, 2H, CH₂), 4.64 (s, 2H, PhCH₂), 5.66 (t, J = 7.8 Hz, 1H, NCH), 6.87-6.95 (m, 2H, Ar), 6.99 (br s, 1H, Ar), 7.23-7.41 (m, 5H, Ar), 8.06 (t, J = 7.7 Hz, 1H, Ar), 8.14-8.18
25 (m, 1H, Ar), 8.26-8.31 (m, 1H, Ar), 11.24 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.66, 34.09, 50.62, 55.46, 63.72, 76.69, 111.86, 112.46, 119.83, 122.47, 126.94, 128.18, 128.67, 130.28, 133.08, 135.79, 136.38, 144.36, 147.69, 148.68, 162.99, 165.69, 166.18. Anal. Calcd for C₂₇H₂₅N₃O₈: C, 62.42; H, 4.85; N, 8.09. Found: C, 62.12; H, 4.92; N, 7.82.

EXAMPLE 20

3-(3-Aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide

A mixture of *N*-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)-propionamide (1.32 g, 2.54 mmol) and 10% Pd/C (230 mg) in ethyl acetate/methanol (150 mL each) was shaken under 50-60 psi of H₂. After 3 days, the suspension was filtered through a pad of Celite, and the pad washed with methanol (75 mL) and methylene chloride (75 mL). The filtrate was concentrated *in vacuo* to give an oil. The oil was stirred with ether (20 mL) to afford 3-(3-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxypropionamide as a yellow solid (650 mg, 64% yield): mp, 143.0-145.0 °C; ¹H NMR (DMSO-d₆) δ 1.39 (t, *J* = 6.9 Hz, 3H, CH₃), 3.16 (d, *J* = 7.8 Hz, 2H, CH₂), 3.79 (s, 3H, CH₃), 4.05 (q, *J* = 6.9 Hz, 2H, CH₂), 5.68 (t, *J* = 7.8 Hz, 1H, NCH), 6.55 (br s, 2H, NH₂), 6.98-7.08 (m, 5H, Ar), 7.47-7.53 (m, 1H, Ar), 8.88 (br s, 1H, OH), 10.66 (1H, NH); ¹³C NMR (DMSO-d₆) δ 14.70, 34.37, 49.65, 55.47, 63.75, 108.64, 110.68, 111.77, 112.39, 119.61, 121.40, 131.69, 132.03, 135.19, 146.48, 147.65, 148.47, 166.14, 167.81, 169.18; Anal Calcd for C₂₀H₂₁N₃O₆: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.76; H, 5.21; N, 10.30.

EXAMPLE 21

N-Hydroxy-N-methyl-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindol-1-yl)propionamide

N-Hydroxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindol-1-yl)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindol-1-yl)propanoic acid (1.0 g, 2.8 mmol), carbonyldiimidazole (500 mg, 3.1 mmol) and *N*-methyl-hydroxylamine hydrochloride (300 mg, 3.5 mmol) in tetrahydrofuran (10 mL) to afford *N*-hydroxy-*N*-methyl-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindol-1-yl)propionamide as a white solid (650 mg, 61% yield): mp, 122.0-124.5 °C; ¹H NMR (CDCl₃) δ 1.43 (t, *J* = 7.0 Hz, 3H, CH₃), 3.14 (s, 3H, NCH₃), 3.37-3.48 (m, 2H, CH₂), 3.86 (s, 3H, CH₃), 4.02 (q, *J* = 7.0 Hz, 2H, CH₂), 4.11 (d, *J* = 17.2 Hz, NCHH), 4.51 (d, *J* = 17.2 Hz, 1H, NCHH), 5.95 (dd, *J* = 6.5, 10.9 Hz, 1H, NCH), 6.83-6.97 (m, 3H, Ar), 7.34-7.55 (m, 3H, Ar), 7.81 (d, *J* = 7.1 Hz, 1H, Ar), 9.44 (br s, 1H, OH); ¹³C NMR (DMSO-d₆) δ 14.71, 36.04, 38.11,

48.14, 52.36, 55.95, 64.52, 111.42, 112.42, 119.45, 122.95, 123.63, 128.06, 130.57, 131.88, 141.72, 148.65, 149.18, 170.00, 170.17; Anal Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.56; H, 6.26; N, 7.09.

EXAMPLE 22

5 *N*-Hydroxy-3-(3-(1-methyl)ethoxy-4-methoxyphenyl)-3-(1-oxoisindolin-yl)propionamide

N-Hydroxy-3-(3-(1-methyl)ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide was prepared by the procedure of Example 1 from 3-(3-(1-methyl)ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propanoic acid (500 mg, 1.35 mmol),
10 carbonyldiimidazole (230 mg, 1.42 mmol) and hydroxylamine hydrochloride (120 mg, 1.75 mmol) in tetrahydrofuran (5 mL) to afford *N*-hydroxy-3-(3-(1-methyl)ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide as a white solid (4.1 g, 79% yield): mp, 173.0-174.0 °C; 1H NMR (DMSO- d_6) δ 1.19 (d, J = 8.2 Hz, 3H, CH_3), 1.23 (d, J = 8.2 Hz, 3H, CH_3), 2.82-2.85 (m, 2H, CH_2), 3.71 (s, 3H, CH_3),
15 4.11 (d, J = 17.5 Hz, NCHH), 4.46-4.58 (m, 2H, CH, NCHH), 5.73 (t, J = 7.5 Hz, 1H, NCH), 6.86-6.93 (m, 3H, Ar), 7.47-7.69 (m, 4H, Ar), 8.83 (br s, 1H, OH), 10.60 (1H, NH); ^{13}C NMR (DMSO- d_6) δ 21.99, 22.09, 35.17, 46.41, 51.35, 55.67, 70.61, 112.48, 115.08, 119.79, 122.97, 123.62, 178.05, 131.51, 132.04, 132.45, 141.83, 146.71, 149.63, 166.23, 167.07; Anal Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 60.58; H, 6.18; N, 6.47.

EXAMPLE 23

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-hydroxyphthalimido)propionamide

3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3-hydroxyphthalimido)propionamide was prepared by the procedure of Example 1 from
25 3-(3-ethoxy-4-methoxyphenyl)-3-(3-hydroxyphthalimido)propanoic acid (0.70 g, 1.8 mmol), carbonyldiimidazole (690 mg, 4.25 mmol) and hydroxylamine hydrochloride (380 mg, 5.47 mmol) in tetrahydrofuran (10 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3-hydroxy-phthalimido)propionamide as a yellow solid (580 mg, 80% yield): mp, 209.0-210.0 °C; 1H NMR (DMSO- d_6) δ 1.31 (t, J =

6.9 Hz, 3H, CH₃), 3.08 (d, *J* = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.97 (q, *J* = 6.9 Hz, 2H, CH₂), 5.62 (t, *J* = 7.9 Hz, 1H, NCH), 6.88 (br s, 2H, Ar), 6.99 (br s, 1H, Ar), 7.18 (d, *J* = 8.3 Hz, 1H, Ar), 7.22 (d, *J* = 7.1 Hz, 1H, Ar), 7.58 (dd, *J* = 7.4, 8.2 Hz, 1H, Ar), 8.88 (br s, 1H, OH), 10.58 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 24.73, 44.31, 59.77, 65.49, 73.77, 121.76, 122.40, 123.84, 124.29, 129.66, 133.41, 141.53, 143.24, 146.04, 157.66, 158.49, 165.49, 176.14, 176.39, 177.51; Anal Calcd for C₂₀H₂₀N₂O₇: C, 60.00; H, 5.03; N, 7.00. Found: C, 59.99; H, 5.08; N, 7.03.

EXAMPLE 24

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-hydroxyphthalimido)propionamide

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-hydroxyphthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(4-hydroxyphthalimido)propanoic acid (4.0 g, 10.4 mmol), carbonyldiimidazole (2.02 g, 12.46 mmol) and hydroxylamine hydrochloride (1.13 g, 16.3 mmol) in tetrahydrofuran (20 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-hydroxyphthal-imido)propionamide as a yellow solid (1.8 g, 44% yield): mp, 143.5-146.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 6.9 Hz, 3H, CH₃), 3.09 (d, *J* = 7.9 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.98 (q, *J* = 6.9 Hz, 2H, CH₂), 5.62 (t, *J* = 7.9 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.09-7.12 (m, 2H, Ar), 7.66-7.69 (m, 1H, Ar), 8.88 (br s, 1H, OH), 10.59 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 24.71, 44.39, 60.08, 65.47, 73.75, 119.72, 121.76, 122.36, 129.66, 130.53, 131.37, 135.32, 141.49, 144.08, 157.68, 158.51, 173.43, 176.09, 177.49; Anal Calcd for C₂₀H₂₀N₂O₇ + 0.35 H₂O: C, 59.07; H, 5.13; N, 6.89. Found: C, 58.84; H, 5.05; N, 7.26.

EXAMPLE 25

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-methylphthalimido)propionamide

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-methylphthalimido)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(3-methylphthalimido)propanoic acid (1.50 g, 3.91

mmol), carbonyldiimidazole (698 mg, 4.30 mmol) and hydroxylamine hydrochloride (330 mg, 4.75 mmol) in tetrahydrofuran (5 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3-methylphthal-imido)propionamide as a white solid (1.4 g, 90% yield): mp, 165.0-166.5 °C; ¹H NMR (DMSO-d₆) δ 1.32 (t, *J* = 6.9 Hz, 3H, CH₃), 2.61 (s, 3H, CH₃), 3.10 (d, *J* = 7.9 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.98 (q, *J* = 7.0 Hz, 2H, CH₂), 5.66 (t, *J* = 7.8 Hz, 1H, NCH), 6.87-6.90 (m, 2H, Ar), 7.02 (br s, 1H, Ar), 7.57-7.69 (m, 3H, Ar), 8.80 (br s, 1H, OH), 10.59 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.71, 16.99, 34.21, 49.95, 55.45, 63.73, 111.72, 112.38, 119.70, 120.76, 127.79, 131.27, 131.67, 134.06, 136.66, 137.29, 147.65, 148.51, 166.06, 167.55, 168.31; Anal Calcd for C₂₁H₂₂N₂O₆ + H₂O: C, 60.57; H, 5.81; N, 6.73. Found: C, 60.83; H, 5.72; N, 6.53.

EXAMPLE 26

3-(3-Acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide

3-(3-Acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxypropion-amide was prepared by the procedure of Example 1 from 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (2.0 g, 4.7 mmol), carbonyldiimidazole (1.14 g, 7.03 mmol) and hydroxylamine hydrochloride (651 mg, 9.37 mmol) in tetrahydrofuran (10 mL) to afford 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxypropionamide as a white solid (1.0 g, 48% yield): mp, 117.0-119.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 6.9 Hz, 3H, CH₃), 2.19 (s, 3H, CH₃), 3.09 (d, *J* = 7.9 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.98 (q, *J* = 7.0 Hz, 2H, CH₂), 5.65 (t, *J* = 7.8 Hz, 1H, NCH), 6.87-6.95 (m, 2H, Ar), 6.99 (br s, 1H, Ar), 7.54 (d, *J* = 6.9 Hz, 1H, Ar), 7.77 (t, *J* = 7.45 Hz, 1H, Ar), 8.41-8.47 (m, 1H, Ar), 8.80 (br s, 1H, OH), 9.71 (s, 1H, NH), 10.59 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 24.69, 34.20, 44.09, 60.04, 65.48, 73.79, 121.78, 122.43, 126.69, 127.97, 129.64, 135.83, 141.00, 141.44, 145.75, 146.38, 157.70, 158.59, 175.97, 177.13, 178.19, 179.22; Anal Calcd for C₂₂H₂₃N₃O₇ + 0.3 H₂O: C, 59.14; H, 5.32; N, 9.40. Found: C, 59.32; H, 5.33; N, 9.02.

EXAMPLE 27***3-(4-Acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide***

3-(4-Acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide was prepared by the procedure of Example 1 from 3-(4-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (2.0 g, 4.7 mmol), carbonyldiimidazole (836 mg, 5.16 mmol) and hydroxylamine hydrochloride (391 mg, 5.63 mmol) in tetrahydrofuran (8 mL) to afford 3-(4-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide as a yellow solid (0.9 g, 43% yield): mp, 138.0-140.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, J = 6.9 Hz, 3H, CH₃), 2.12 (s, 3H, CH₃), 3.09 (d, J = 7.9 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.98 (q, J = 6.9 Hz, 2H, CH₂), 5.64 (t, J = 7.8 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.77-7.86 (m, 2H, Ar), 8.17 (br s, 1H, Ar), 8.80 (br s, 1H, OH), 10.58 (br s, 2H, 2NH); ¹³C NMR (DMSO-d₆) δ 14.69, 24.18, 34.27, 50.15, 55.43, 63.69, 111.68, 112.26, 112.46, 119.63, 123.11, 124.37, 124.79, 131.26, 132.76, 114.87, 147.65, 148.48, 165.98, 167.26, 169.22; Anal Calcd for C₂₂H₂₃N₃O₇: C, 59.86; H, 5.25; N, 9.52. Found: C, 59.49; H, 5.24; N, 9.40.

EXAMPLE 28***3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)propionamide***

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]-isoindol-2'-yl)propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)propanoic acid (1.50 g, 3.57 mmol), carbonyldiimidazole (609 mg, 3.76 mmol) and hydroxylamine hydrochloride (287 mg, 4.13 mmol) in tetrahydrofuran (8 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)-propionamide as a yellow solid (1.14 g, 74% yield): mp, 160.0 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, J = 6.9 Hz, 3H, CH₃), 3.15 (d, J = 7.8 Hz,

2H, CH₂), 3.72 (s, 3H, CH₃), 3.99 (q, *J* = 7.0 Hz, 2H, CH₂), 5.72 (t, *J* = 7.7 Hz, 1H, NCH), 6.88-7.07 (m, 3H, Ar), 7.71-7.88 (m, 3H, Ar), 8.15 (d, *J* = 8.0 Hz, 1H, Ar), 8.37 (d, *J* = 8.2 Hz, 1H, Ar), 8.78 (m, 2H, OH, Ar), 10.62 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.70, 34.40, 50.12, 55.44, 63.72, 111.72, 112.36, 118.39, 119.68, 122.79, 126.22, 127.09, 128.84, 129.16, 129.88, 130.75, 131.30, 135.48, 136.18, 147.70, 148.51, 168.09, 168.13, 168.89; Anal Calcd for C₂₄H₂₂N₂O₆ + 0.4 H₂O: C, 65.27; H, 5.20; N, 6.34. Found: C, 65.30; H, 5.17; N, 6.46.

EXAMPLE 29

3-(4-tert-Butylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide

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3-(4-tert-Butylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide was prepared by the procedure of Example 1 from 3-(4-tert-butylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (2.0 g, 4.7 mmol), carbonyldiimidazole (800 mg, 4.93 mmol) and hydroxylamine hydrochloride (377 mg, 5.43 mmol) in tetrahydrofuran (10 mL) to afford 3-(4-tert-butylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-propionamide as a white solid (1.77 g, 85% yield): mp, 127.5-129.5 °C; ¹H NMR (DMSO-d₆) δ 1.24-1.44 (m, 12H, 4CH₃), 3.09 (d, *J* = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.97 (q, *J* = 6.9 Hz, 2H, CH₂), 5.66 (t, *J* = 7.8 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.01 (br s, 1H, Ar), 7.76-7.87 (m, 3H, Ar), 8.79 (br s, 1H, OH), 10.59 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.73, 30.76, 34.29, 35.48, 50.14, 55.46, 63.72, 111.69, 112.27, 119.59, 119.98, 123.07, 128.75, 131.28, 131.45, 131.55, 147.69, 148.49, 158.32, 166.07, 167.53, 167.85; Anal Calcd for C₂₄H₂₈N₂O₆: C, 65.44; H, 6.41; N, 6.36. Found: C, 64.34; H, 6.29; N, 7.04.

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EXAMPLE 30

3-(3,4-dimethoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]-isoindol-2'-yl)propionamide

3-(3,4-Dimethoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)propionamide was prepared by the procedure of Example 1 from 3-(3,4-dimethoxyphenyl)-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)propanoic acid (0.90 g, 2.2 mmol), carbonyldiimidazole (382 mg, 2.36 mmol) and hydroxylamine hydrochloride (180 mg, 2.59 mmol) in tetrahydrofuran (10 mL) to afford 3-(3,4-dimethoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)-propionamide. as a yellow solid (150 mg, 15% yield): mp, 218.0-220.0°C; ¹H NMR (DMSO-d₆) δ 3.17 (d, J = 7.8 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.75 (s, 3H, CH₃), 5.74 (t, J = 7.8 Hz, 1H, NCH), 6.88-7.01 (m, 2H, Ar), 7.08 (br s, 1H, Ar), 7.75-7.89 (m, 3H, Ar), 8.17 (d, J = 8.0 Hz, 1H, Ar), 8.40 (d, J = 8.2 Hz, 1H, Ar), 8.78-8.81 (m, 2H, OH, Ar), 10.62 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 34.42, 50.11, 55.48, 111.29, 111.66, 118.35, 119.59, 123.77, 126.21, 127.08, 128.80, 129.13, 129.84, 130.73, 131.38, 135.44, 136.16, 148.35, 148.53, 168.06, 168.09, 168.86; Anal Calcd for C₂₃H₂₀N₂O₆: C, 65.71; H, 4.79; N, 6.66. Found: C, 65.06; H, 4.62; N, 6.44.

EXAMPLE 31

3-(3,4-Dimethoxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide

3-(3,4-Dimethoxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide was prepared by the procedure of Example 1 from 3-(3,4-Dimethoxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropanoic acid (0.83 g, 1.9 mmol), carbonyldiimidazole (501 mg, 3.09 mmol) and hydroxylamine hydrochloride (268 mg, 3.86 mmol) in tetrahydrofuran (10 mL) to afford 3-(3,4-dimethoxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide as a white solid (130 mg, 15% yield): mp, 158.0; ¹H NMR (DMSO-d₆) δ 1.31 (t, J = 7.0

Hz, 3H, CH₃), 3.08 (d, *J* = 7.8 Hz, 2H, CH₂), 3.72 (s, 3H, CH₃), 3.92 (s, 3H, CH₃), 3.94 (s, 3H, CH₃), 3.97 (q, *J* = 7.0 Hz, 2H, CH₂), 5.62 (t, *J* = 7.9 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.00 (br s, 1H, Ar), 7.35-7.38 (m, 1H, Ar), 7.54 (d, *J* = 8.0 Hz, 1H, Ar), 8.78 (br s, 1H, OH), 10.56 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.65, 34.25, 50.03, 55.44, 56.61, 61.73, 63.71, 105.66, 111.74, 112.41, 117.11, 119.52, 119.68, 121.53, 123.48, 131.33, 147.61, 148.49, 157.65, 165.39, 166.00, 166.82; Anal Calcd for C₂₂H₂₄N₂O₈: C, 59.45; H, 5.44; N, 6.30. Found: C, 58.01; H, 5.32; N, 6.02.

EXAMPLE 32

Tablets, each containing 50 mg of N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindoliny)propionamide, are prepared in the following manner:

Constituents (for 1000 tablets)

	N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindoliny)propionamide	50.0 g
15	lactose	50.7 g
	wheat starch	7.5 g
	polyethylene glycol 6000	5.0 g
	talc	5.0 g
20	magnesium stearate	1.8 g
	demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, talc, magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 mL of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

EXAMPLE 33

Tablets, each containing 100 mg of N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide, can be prepared in the following manner:

Constituents (for 1000 tablets)

	N-hydroxy-3-(3,4-dimethoxy- phenyl)-3-phthalimido- propionamide	100.0 g
5	lactose	100.0 g
	wheat starch	47.0 g
	magnesium stearate	3.0 g

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, lactose, magnesium stearate and half of the starch then are
10 mixed. The other half of the starch is suspended in 40 mL of water and this suspen-
sion is added to 100 mL of boiling water. The resulting paste is added to the pulveru-
lent substances and the mixture is granulated, if necessary with the addition of water.
The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh
width and compressed to form tablets of approximately 6 mm diameter which are
15 concave on both sides.

EXAMPLE 34

Tablets for chewing, each containing 75 mg of 3-(3-ethoxy-4-methoxyphenyl)-N-
hydroxy-3-phthalimidopropionamide, can be prepared in the following manner:

	<u>Composition (for 1000 tablets)</u>	
20	3-(3-ethoxy-4-methoxyphenyl)- N-hydroxy-3-phthalimido- propionamide	75.0 g
	mannitol	230.0 g
	lactose	150.0 g
25	talc	21.0 g
	glycine	12.5 g
	stearic acid	10.0 g
	saccharin	1.5 g
30	5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin
solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced
through a sieve of 1.7 mm mesh width. 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-
35 3-phthalimidopropionamide, the glycine and the saccharin are carefully mixed, the
mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is
mixed thoroughly and compressed to form tablets of approximately 10 mm diameter
which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 35

Tablets, each containing 10 mg N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide, can be prepared in the following manner:

Composition (for 1000 tablets)

5	N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide	10.0 g
	lactose	328.5 g
	corn starch	17.5 g
10	polyethylene glycol 6000	5.0 g
	talc	25.0 g
	magnesium stearate	4.0 g
	demineralized water	q.s.

- 15 The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active imide ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 mL of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 mL of water. The resulting paste is added to the pulverulent substances, and the whole is
- 20 mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 36

- 25 Gelatin dry-filled capsules, each containing 100 mg of N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide, can be prepared in the following manner:

Composition (for 1000 capsules)

30	N-benzyloxy-3-(3-cyclopentylidene-methyl-4-methoxyphenyl)-3-phthalimido-propionamide	100.0 g
	microcrystalline cellulose	30.0 g
	sodium lauryl sulfate	2.0 g
35	magnesium stearate	8.0 g

The sodium lauryl sulfate is sieved into the N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-phthalimidopropionamide through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again

intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 mg each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 37

5 A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

	3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide	5.0 g
10	sodium chloride.....	22.5 g
	phosphate buffer pH 7.4.....	300.0 g
	demineralized water	to 2500.0 mL

15 3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide is dissolved in 1000 mL of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 mL with water. To prepare dosage unit forms, portions of 1.0 or 2.5 mL each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 mg of imide).

EXAMPLE 38

20 **3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-dimethylaminophthalimido)-propionamide**

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-dimethylaminophthalimido)-propionamide was prepared by the procedure of Example 1 from 3-(3-ethoxy-4-methoxyphenyl)-3-(3-dimethylaminophthalimido)propanoic acid (0.31 g, 0.75 mmol),
 25 carbonyldiimidazole (140 mg, 0.86 mmol) and hydroxylamine hydrochloride (66 mg, 0.95 mmol) in tetrahydrofuran (5 mL) to afford 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-dimethylaminophthalimido)propionamide as a yellow solid (280 mg, 87% yield): mp, 187.0-188.6 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, J = 7.0 Hz, 3H, CH₃), 3.01 (s, 6H, CH₃), 3.08 (d, J = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.97 (q, J =
 30 6.9 Hz, 2H, CH₂), 5.63 (t, J = 7.9 Hz, 1H, NCH), 6.88 (br s, 2H, Ar), 7.00 (br s, 1H, Ar), 7.19 (m, 2H, Ar), 7.57 (dd, J = 7.1, 8.3 Hz, 1H, Ar), 8.78 (br s, 1H, OH), 10.57 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 14.66, 34.42, 42.96, 49.88, 55.45, 63.72,

111.75, 112.41, 112.71, 113.74, 119.63, 122.32, 131.61, 133.94, 134.92, 147.60, 148.43, 149.75, 166.11, 166.76, 167.56; Anal Calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.89; N, 9.83. Found: C, 61.79; H, 5.90; N, 9.58.

5

EXAMPLE 39**3-(6,8-Dioxo(2H--1,3-dioxolano[4,5-e]isoindolin-7-yl))-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide**

3-(6,8-Dioxo(2H--1,3-dioxolano[4,5-e]isoindolin-7-yl))-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide was prepared by the procedure of Example 1 3-(6,8-dioxo(2H--1,3-dioxolano[4,5-e]isoindolin-7-yl))-3-(3-ethoxy-4-methoxyphenyl)propanoic acid (1.20 g, 2.90 mmol), carbonyldiimidazole (517 mg, 3.19 mmol) and hydroxylamine hydrochloride (255 mg, 3.66 mmol) in tetrahydrofuran (8 mL) to afford 3-(6,8-Dioxo(2H--1,3-dioxolano[4,5-e]isoindolin-7-yl))-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide as an off-white solid (960 mg, 77% yield): mp, 203.0° C (decomposed); 1H NMR (DMSO- d_6) δ 1.31 (t, J = 6.6 Hz, 3H, CH_3), 3.08 (d, J = 7.5 Hz, 2H, CH_2), 3.72 (s, 3H, CH_3), 3.97 (q, J = 6.9 Hz, 2H, CH_2), 5.62 (t, J = 7.3 Hz, 1H, NCH), 6.33 (s, 2H, CH_2), 6.89 (br s, 2H, Ar), 6.99 (br s, 1H, Ar), 7.22 (d, J = 7.7 Hz, 1H, Ar), 7.37 (d, J = 7.6 Hz, 1H, Ar), 8.80 (br s, 1H, OH), 10.58 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6) δ 14.67, 34.18, 50.12, 55.46, 63.75, 104.31, 110.73, 111.76, 111.96, 112.37, 118.56, 119.62, 124.15, 131.25, 143.56, 147.66, 148.53, 154.12, 164.74, 165.99, 166.59; Anal Calcd for $C_{21}H_{20}N_2O_8 + 1 H_2O$ C, 56.50; H, 4.97; N, 6.28. Found: C, 56.22; H, 4.63; N, 6.28.

25

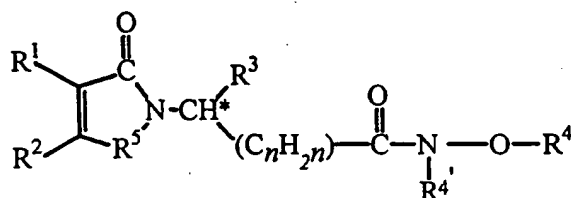
Example 40**3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3,4-dimethylphthalimido)propionamide**

3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3,4-dimethylphthalimido)propionamide was prepared by the procedure of Example 16 N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3,4-dimethylphthalimido)propanamide (0.63 g, 1.25 mmol),

- Pd(OH)₂/C (100 mg) and hydrogen (50 psi) in ethyl acetate and methanol (30 mL each) to afford 3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3,4-dimethylphthalimido)propionamide as a white solid (430 mg, 84% yield): mp, 197.0-202.5 °C; ¹H NMR (DMSO-d₆) δ 1.31 (t, *J* = 7.2 Hz, 3H, CH₃), 2.35 (s, 3H, CH₃), 2.56 (s, 3H, CH₃), 3.09 (d, *J* = 7.9 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃), 3.97 (q, *J* = 6.9 Hz, 2H, CH₂), 5.65 (t, *J* = 7.9 Hz, 1H, NCH), 6.89 (br s, 2H, Ar), 7.00 (br s, 1H, Ar), 7.59 (br s, 2H, Ar), 8.78 (br s, 1H, OH), 10.56 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 13.22, 14.65, 19.33, 34.21, 49.88, 55.43, 63.72, 111.75, 112.40, 119.62, 120.39, 127.76, 129.33, 131.36, 134.71, 136.50, 145.13, 147.62, 148.48, 166.02, 167.32, 168.65; Anal Calcd for C₂₂H₂₄N₂O₆ + 0.3 H₂O: C, 63.24; H, 5.93; N, 6.70. Found: C, 63.11; H, 5.88; N, 6.67.

What is claimed is:

1. A hydroxamic acid derivative selected from the group consisting of (a) compounds of the formula:



wherein

each of R¹ and R², when taken independently of each other, is hydrogen, lower alkyl, or R¹ and R², when taken together, together with the depicted carbon atoms to which each is bound, is *o*-phenylene, *o*-naphthylene, or cyclohexene-1,2-diyl, unsubstituted or substituted with 1 to 4 substituents each selected independently from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, C₄-C₆-cycloalkylidenemethyl, C₃-C₁₀-alkylidenemethyl, indanyloxy, and halo;

R³ is phenyl substituted with from one to four substituents selected from the group consisting of nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, and halo;

R⁴ is hydrogen, alkyl of 1 to 10 carbon atoms, phenyl, or benzyl;

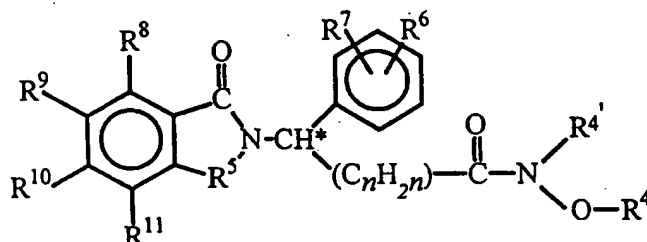
R^{4'} is hydrogen or alkyl of 1 to 6 carbon atoms;

R⁵ is -CH₂-, -CH₂-CO-, -CO-, -SO₂-, -S-, or -NHCO-; and

n has a value of 0, 1, or 2; and

(b) the acid addition salts of said compounds which contain a nitrogen atom capable of being protonated.

2. A hydroxamic acid derivative according to claim 1 wherein said compound has the formula:



in which

each of R^4 and $R^{4'}$ independently is hydrogen or alkyl of 1 to 4 carbon atoms;

R^5 is $-\text{CH}_2-$, $-\text{CH}_2\text{CO}-$, or $-\text{CO}-$;

each of R^6 and R^7 , independently of the other, is nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms, or halo;

each of R^8 , R^9 , R^{10} , and R^{11} , independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo; and

n has a value of 1.

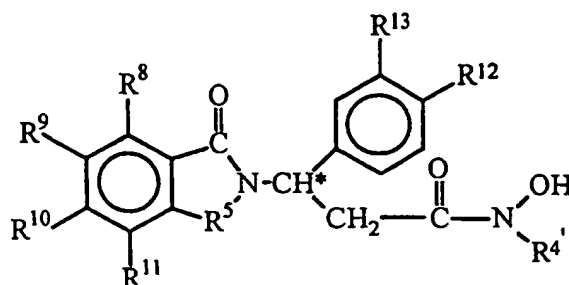
3. A hydroxamic acid derivative according to claim 2 wherein each of R^8 , R^9 , R^{10} , and R^{11} is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms.

4. A hydroxamic acid derivative according to claim 2 wherein one of R^8 , R^9 , R^{10} , and R^{11} is amino and the remaining of R^8 , R^9 , R^{10} , and R^{11} , are hydrogen.

5. A hydroxamic acid derivative according to claim 2 wherein one of R^8 , R^9 , R^{10} , and R^{11} is alkyl and the remaining of R^8 , R^9 , R^{10} , and R^{11} , are hydrogen.

6. A hydroxamic acid derivative according to claim 2 wherein R^8 , R^9 , R^{10} , and R^{11} are hydrogen.

7. A hydroxamic acid derivative according to claim 1 wherein said compound has the formula:



in which

$R^{4'}$ is hydrogen or alkyl of 1 to 4 carbon atoms;

R^5 is C=O or CH₂;

each of R^{12} and R^{13} , independently of the other alkoxy of 1 to 4 carbon atoms, cycloalkoxy of 3 to 6 carbon atoms; C₄-C₆-cycloalkylidenemethyl, C₂-C₁₀-alkylidenemethyl, C₆-C₁₀-bicycloalkoxy, or indanyloxy; and

each of R^8 , R^9 , R^{10} , and R^{11} , independently of the others, is hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxyl, carboxyl, hydroxyl, amino, alkylamino, dialkylamino, acylamino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, and halo.

8. The hydroxamic acid derivative according to claim 7 wherein $R^{4'}$ is Hydrogen.

9. The hydroxamic acid derivative according to claim 7 wherein each of R^8 , R^9 , R^{10} , and R^{11} is hydrogen, halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms.

10. A hydroxamic acid derivative according to claim 7 wherein one of R^8 , R^9 , R^{10} , and R^{11} is -amino, hydroxyl, or alkyl and the remaining of R^8 , R^9 , R^{10} , and R^{11} , are hydrogen.

11. A hydroxamic acid derivative according to claim 1 wherein said compound is selected from the group consisting of 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindolinyl)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-methoxy-3-(1-oxoisindolinyl)propionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-

phthalimidopropionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-nitrophthalimido)propionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-methylphthalimido)propionamide, 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[f]isoindol-2-yl)propionamide, N-hydroxy-3-{3-(2-propoxy)-4-methoxyphenyl}-3-phthalimidopropionamide, 3-(3-ethoxy-4-methoxyphenyl)-3-(3,6-difluorophthalimido)-N-hydroxypropionamide, 3-(4-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-aminophthalimido)-3-(3-methoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-aminophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-aminophthalimido)-3-(3-cyclopentoxy-4-methoxyphenyl)-N-hydroxypropionamide, N-hydroxy-3-(3,4-dimethoxyphenyl)-3-(1-oxoisindolinyl)propionamide, N-benzyloxy-3-(3-ethoxy-4-methoxyphenyl)-3-(3-nitrophthalimido)propionamide; 3-(3-cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(1-oxoisindolinyl)propionamide, 3-(3-methylphthalimido)-3-(3-cyclopentoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(4-methylphthalimido)-3-(3-cyclopentoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-hydroxyphthalimido)-3-(3-cyclopentoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(4-hydroxyphthalimido)-3-(3-cyclopentoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-methylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(4-methylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-hydroxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(4-hydroxyphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, N-Hydroxy-N-methyl-3-(3-ethoxy-4-methoxyphenyl)-3-(1-oxoisindolinyl)propionamide, 3-(3-Cyclopentyloxy-4-methoxyphenyl)-N-hydroxy-3-(4-ethylphthalimido)propionamide, 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-hydroxyphthalimido)propionamide, 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(4-hydroxyphthalimido)propionamide, 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(3-methylphthalimido)propionamide, 3-(3-Acetoamido-phthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(4-Acetoamido-phthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide, 3-(3-Ethoxy-4-methoxyphenyl)-N-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindol-2'-yl)propionamide, 3-(4-

tert-Butylphthalimido)-3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxyprop-ionamide, 3-(3,4-dimethoxyphenyl)-*N*-hydroxy-3-(1,3-dioxo-2,3-dihydro-1H-benzo[*e*]-isoindol-2'-yl)propionamide, 3-(3,4-Dimethoxyphthalimido)-3-(3-ethoxy-4-methoxy-phenyl)-*N*-hydroxypropionamide, 3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3-dimethylaminophthalimido)-propionamide, 3-(6,8-Dioxo(2H-1,3-dioxolano[4,5-*e*]isoindolin-7-yl))-3-(3-ethoxy-4-methoxyphenyl)-*N*-hydroxypropionamide, and 3-(3-Ethoxy-4-methoxyphenyl)-*N*-hydroxy-3-(3,4-dimethylphthalimido)propionamide.

12. The method of reducing undesirable levels of $\text{TNF}\alpha$ in a mammal which comprises administering thereto an effective amount of a hydroxamic acid derivative according to claim 1.

13. A pharmaceutical composition comprising a quantity of a hydroxamic acid derivative according to claim 1 sufficient upon administration in a single or multiple dose regimen to reduce levels of $\text{TNF}\alpha$ in a mammal in combination with a carrier.

14. A pharmaceutical composition comprising a quantity of a hydroxamic acid derivative according to claim 1 sufficient upon administration in a single or multiple dose regimen to inhibit undesirable levels of matrix metalloproteinases in a mammal in combination with a carrier.

15. The method of inhibiting undesirable levels of matrix metalloproteinases in a mammal which comprises administering thereto an effective amount of a hydroxamic acid derivative according to claim 1.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US98/15868

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/40, 31/425, 31/445, 31/515

US CL : 514/423, 372, 270, 315, 247

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/423, 372, 270, 315, 247

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - A	Database Chemical Abstracts on STN, TELEGDI et al, AN 1991:38337, "Hydroxamic acids as organic catalysts of enzyme activity." Magy. Kem. Goly. (1990), 96(6), 285-6, see entire abstract.	1-14 ----- 15
X - A	Database Chemical Abstracts on STN, NIKOLIC et al, AN 1995:463886, "QSPR and QSAR study of phthalimidohydroxamic acids." Acta Pharm. (Zagreb) (1995), 45(1), 15-24, see entire abstract.	1-14 --- 15
X - A	Database Chemical Abstracts on STN, MATOKEVIC-SOSA et al, AN 1994:271087, "Synthesis and mitodepressive activity of some phthalimidoalkanehydroxamic acids." Acta. Pharm. (Zagreb), (1993), 43(3), 185-194, see entire abstract.	1-14 ----- 15

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
03 NOVEMBER 1998	02 DEC 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer <i>Keith Macmillan</i> KEITH MACMILLAN For Telephone No. (703) 308-1235